Relative Energy Index of Microembolic Signal Can Predict Malignant Microemboli

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Background and Purpose—Microembolic signals (MES) found on transcranial Doppler range from harmless air bubbles to large, solid, particulate emboli from the heart and large vessels. The presence of MES is not always associated with poor clinical outcome. The purpose of our study was to determine whether the relative energy index of MES measured by power M-mode Doppler can distinguish malignant from benign MES and to identify patients with worse prognosis.

Methods—We prospectively collected transcranial Doppler emboli monitoring data from patients with symptomatic carotid stenosis presenting with TIA or ischemic stroke. For each patient, we calculated the relative energy index of MES and categorized those >1.0 as malignant MES. We compared the clinical characteristics, number, and volume of diffusion-weighted imaging lesions, and degree of stenosis and plaque characteristics on CT angiogram of patients with malignant and benign MES.

Results—We enrolled 92 patients, 29 with TIA and 63 with stroke, within 48 hours of symptom onset. Twenty-six patients had a total of 319 MES; of these, 82.4% were benign and were 17.6% malignant. Malignant MES traveled further within intracranial vessels than benign MES. The 9 patients with >1 malignant MES had significantly larger baseline diffusion-weighted imaging lesion volume, had a higher prevalence of intraluminal thrombus on CT angiogram of the neck and plaque ulceration, and were more likely to have a poor clinical outcome (modified Rankin Score ≥2) than those with benign MES (OR, 6.5; 95% CI, 1.47–28.68). The presence of malignant MES led to the institution of more aggressive secondary prevention measures.

Conclusions—Power M-mode transcranial Doppler identifies a subgroup of patients with malignant MES. These signals are more frequent in longer arterial trajectory. Patients with malignant MES have larger baseline infarcts, a higher prevalence of intraluminal thrombus or ulcerated plaque in the carotid artery, and worse clinical outcome. (Stroke. 2010;41:700-706.)

Key Words: malignant emboli ▶ microemboli ▶ transcranial Doppler

Transcranial Doppler (TCD) is gradually gaining acceptance as a monitoring tool to detect embolic signals often referred to as microemboli signals (MES).1 These MES correlate well with true emboli in animal models2 and are most frequently identified in the setting of large vessel atherosclerotic disease, such as carotid stenosis.3 There have been reports that the presence of MES is an independent predictor of future stroke in patients with symptomatic4 and asymptomatic carotid stenosis.5,6 However, not all studies have demonstrated the anticipated association between MES and clinical outcome.7,8

TCD MES span a broad spectrum, ranging from harmless air bubbles produced by artificial valves to the opposite extreme in which large, solid, particulate emboli from the heart and large vessels traverse the intracranial vasculature. If TCD can distinguish the benign from the malignant MES, then it would be useful for predicting outcome and may influence therapy. Ackerstaff et al10 reported that TCD emboli variables called “macroembolus” and “massive air embolism” were associated with poor outcome within 7 days after stent deployment. They applied the definition of macroembolus as an embolus that partially or completely obstructed the middle cerebral artery (MCA) main stem for a period of several seconds to minutes.10 That study was the first to define the concept of malignant embolus. However, just applying this definition to MES may not be enough to define the size/prognosis of an embolus. This goal has been difficult to reach to date, even though MES have been shown to be associated with the morphology of plaque surface.11,12 Considerable work has been performed trying to distinguish between solid emboli vs air composition.13,14 In addition, several studies have attempted to measure the size of emboli by their specific characteristics.15 These efforts have been limited by the type of technology used in emboli detection.

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because most studies relied on single-gate spectrogram TCD, which has limited sample volume that covers only a small part of the travel path of an embolus. Transcranial power M-mode Doppler (PMD) is now available with digital TCD that simultaneously sample 33 gates over 60 mm of intracranial space. The wide range of sampling signals of PMD could provide information such as arterial trajectory, multigate travel time, maximal duration, travel length, and velocity of embolus, which would not be measured by the spectrogram alone.

Quantity of the microemboli, such as the presence or frequency detected by transcranial Doppler, has been considered to be the only variable being correlated with the risk of recurrent stroke. Our aim is to determine if the quality of microemboli measured by power M-mode Doppler represents a malignant type of MES in terms of volume of diffusion-weighted imaging (DWI) lesion, 3-month clinical outcome, pattern of carotid plaque based on CT angiogram for neck, and recurrent stroke.

Materials and Methods
We prospectively collected TCD emboli monitoring data from patients who participated in a prospective cohort studies, either TASC (Transcranial Doppler and Symptomatic Carotid Disease study) or VISION (Vascular Imaging of Acute Stroke for Identifying Predictors of Clinical Outcome and Recurrent Ischemic Events) trials, at a single academic center between May 1, 2002 and December 31, 2006. Among them, patients who had carotid stenosis (>50% stenosis), occlusion, or unstable carotid plaque were investigated. The patients underwent bilateral hemisphere TCD emboli monitoring for 1 hour within 48 hours of their clinical presentation. Two registered sonographers had been practicing during that period; also, 2 experienced stroke neurologists were involved. Ten (10/102; 9.8%) patients were excluded from study because of inadequate temporal bone window. The research protocol involved. Ten (10/102; 9.8%) patients were excluded from study because of inadequate temporal bone window. The research protocol.

PMD (100 mol/L; Spencer Technologies) was used to acquire 2-MHz spectral single-gate TCD information at a specific depth and power M-mode information from 33 sample volumes placed at 2-mm intervals from 24 to 88 mm depth of insonation. Probe fixation using a head frame (Marc 500; Spencer Technologies) was used for monitoring. One proximal MCA segment was insonated and, when possible, ipsilateral anterior cerebral artery or internal carotid artery were used for PMD display. The insonation depth for spectrogram recording was between 45 and 65 mm for the ipsilateral MCA. Semiautomated algorithm saved every possible MES for a 1-hour period. The MES were reviewed by an experienced neurosonologist blinded to all clinical and imaging information.

We measured several parameters of MES: maximum duration (sec) of MES in a 3-mm gate, MES maximum intensity with adjustment of the intensity of the background blood flow (MaxI), multigate travel time, distance of MES travel, and the velocity (cm/sec) of MES. In addition, we listed the arterial trajectory of MES on PMD display. Arterial trajectory of MES means the pathway MES travel around in the intracranial arterial system. For instance, it can be M1–M2, or M1 to branch, or internal carotid artery to branch. All information from the M-mode 33 gates provide the MES travel pathway, which are not necessarily correlated with the duration of MES, because the duration of MES can be affected by velocity of MES, hemodynamic status of patient, and size of MES. To describe the MES quality that represents malignant MES, we derived the relative energy index of microembolus (REIM) as REIM = MaxI (maximal intensity) × MaxD (maximal duration) (Figure 1). To estimate the diameter of the embolus and define the cut-off value of REIM for malignant microembolus, we used the following relationship:

\[ m^2c^4 = E^2 - p^2c^2 \]

Where \( E \) is the energy, \( m \) is the mass, \( c \) is the speed of light, and \( p \) is the 3-dimensional momentums of the MES. If the velocity of the particle is much smaller than \( c \), then \( E \) can be approximated as \( E = mc^2 \). If the embolus is considered to be a sphere, then \( m \) can be calculated as \( m = 4/3 \pi r^3 \). If \( p \) is constant, then the energy can be considered proportionate to the cubic radius of an embolus (ie, \( E \propto r^3 \)), assuming that the minimal diameter of embolus that can be detected by TCD is 80 \( \mu m \) and the maximal diameter of embolus that can enter the MCA main trunk is 3000 \( \mu m \). We compared REIM with the log radius of embolus ranging from 40 \( \mu m \) to 1500 \( \mu m \). The embolus, with REIM 1.0 that represents 500 \( \mu m \) of diameter of embolus, was considered to be the cut-off value for malignant microembolus because the mean diameter of the penetrating artery of MCA branch is <500 \( \mu m \). Figure 2 shows that the distribution of
emboli based on the diameter and shows that the diameter of emboli ranged from 80 μm to 400 μm (233/319; 73.0%) when REIM 1.0 represented a 500-μm diameter embolus. Therefore, the cut-off value of REIM 1.0 was arbitrarily used to identify the malignant microemboli.

The patients were categorized into 2 subgroups based on the presence of malignant MES: patients with benign MES only (benign MES group) vs patients with >1 malignant MES (malignant MES group). Clinical characteristics, initial NIHSS, 90-day NIHSS, modified Rankin Scale score at 90 days, DWI lesion volume and number, the characteristics of the plaque on baseline CTA of the neck, and recurrent stroke/TIA in 90 days were compared between malignant MES and benign MES groups. Also, comparison of early anticoagulation or early carotid endarterectomy/stent between 2 groups had been performed. The DWI lesion volumes were measured by computer-assisted volumetric analysis using custom software that incorporated a neighborhood-connected region growing threshold segmentation method (ITK; National Library of Medicine). CTA of the neck was performed on 64-row multidetector CT (Siemens). The CTA results were reviewed by 2 stroke neurologists and 2 neuroradiologists by consensus on a remote research PACS station. 

Reviewers were blinded to the clinical data and any imaging of the head. If there was a plaque, then the degree of stenosis was measured by the NASCET criteria. The plaque length was measured electronically as the maximum longitudinal dimension, whereas the thickness was measured at the maximum stenosis in the axial sections. The density was qualitatively assessed as hypodense, isodense, or heterogeneous compared to that of neck muscles. The degree of calcification was classified as mild, moderate, or extensive if <30%, 30% to 70%, or >70% of the plaque was calcified, respectively. The plaque surface was classified as smooth, irregular, and ulcerated. The ulcer was defined as focal extension of the contrast beyond the lumen by at least 1 mm. Intraluminal thrombus was defined as a filling defect within the lumen completely surrounded by contrast on at least 2 contiguous axial source images.

Demographics of study population and MES counts were reported using descriptive statistics. Student t test was used to compare the parameters between benign MES and malignant MES. The χ² test was applied to compare the arterial trajectory, the patterns of carotid plaque on CT angiogram, and recurrent vascular events. Student t test was used to evaluate the statistical difference of emboli count and DWI lesion volume. Mann-Whitney U tests was applied to compare the NIHSS scores and modified Rankin Scale scores. Statistical significance thresholds were established for all test, with P ≤0.05 indicating difference. All statistical tests were performed using SPSS (SPSS version 11.5; SPSS).

### Results

Ninety-two patients with carotid disease had TIA/stroke and underwent TCD emboli monitoring within 48 hours of onset of symptoms. Mean age was 67.7 ± 13.1 years and 69 patients (75.0%) were men. Ten patients (10.9%) were excluded because of inadequate temporal bone window. Median baseline NIHSS was 2 (interquartile range [IQR], 0–4). Twenty-nine patients (31.5%) had TIA and 63 (68.5%) patients had stroke. The mean time from symptoms onset to clinical evaluation was 12.8 ± 6.4 hours. The TCD monitoring for MES was performed at median time of 16.4 hours (range, 2.5–47 hours) from onset of symptoms. Twenty-six patients (26/92; 28.3%; mean age, 63.4 ± 17.3 years) had positive MES on PDM, and a total of 319 MES were detected by PDM (mean MES, 3.55; ±SD 10.6; median, 0; IQR, 0–1).

Fifty-six MES (56/319; 17.6%) with REIM > 1.0 were considered to be malignant MES. The characteristics of malignant MES are summarized in Table 1. Malignant MES had greater REIM, MaxI (dB), maximum duration (ms), multigate travel time (ms), and distance of MES travel (mm) than benign emboli (REIM, 2.1 ± 0.2 vs 0.4 ± 0.2; MaxI, 19.3 ± 5.5 vs 8.5 ± 3.2; maximum duration, 104.8 ± 26.3 vs 52.9 ± 12.7; multigate travel time, 168.3 ± 64.0 vs 76.4 ± 36.4; distance of MES travel, 37.5 ± 8.6 vs 17.8 ± 9.1; P < 0.001).

Figure 3 shows an example of a typical malignant MES and benign MES. There was no statistically significant differences found with the velocity of MES (cm/sec) between malignant MES and benign MES (24.6 ± 9.4 vs 25.2 ± 16.4; P = 0.73). The mean diameter (μm) of malignant MES was significantly larger than benign MES (1009.1 ± 466.7 μm vs 275.2 ± 98.2 μm; P < 0.001). Malignant MES (51/56; 91.1%) had more frequent M1–M2 arterial trajectories than benign MES (48/263; 18.3%; OR, 45.7; 95% CI, 17.3–120.6; P < 0.001). Benign MES more frequently had only M1 arterial trajectories (123/263; 48.7%) than malignant MES (3/56; 5.4%; OR, 9.1; 95% CI, 3.02–27.72; P < 0.001). Benign MES also had more frequent branch artery trajectories (perforator and only M2; 42/263; 16.0%) than malignant MES.
Nine out of 26 MES-positive patients (34.6%) who had malignant MES were categorized into malignant MES group. Seventeen patients (65.4%; 17/26) who had only benign MES were categorized into the benign MES group. There were no differences between benign and malignant MES groups regarding risk factors for stroke and antiplatelet agent or statin usage before index stroke (Table 1). The baseline clinical stroke severity measured by NIHSS score tended to be higher in the malignant MES group (median, 4; IQR, 1.5–12) than in the benign MES group (median, 2; IQR, 1–5; P=0.218), which was statistically not significant. NIHSS at 90 days was significantly higher in malignant MES group (median, 4; IQR, 1–12) than in the benign MES group (median, 2; IQR, 0–2; P=0.025). Modified Rankin Scale score ≥2 was a poor clinical outcome at 90 days was significantly more common in the malignant MES group (4/9; 44.4%) than in the benign MES group (2/17; 11.8%; P=0.025; OR, 6.5; 95% CI, 1.47–28.68). Total emboli count was significantly higher in the malignant MES group (25.1 ± 22.1) than in the benign MES group (5.3 ± 8.3; P=0.002).

Out of 92 patients, 65 patients (70.7%) underwent MR scan within 48 hours from symptoms onset. All MES-positive patients underwent MRI. Twenty-seven patients (27/92; 29.3%) were not eligible for MR scan because of metals in the body, claustrophobia, obesity, or cardiac pacemaker. The mean time from symptoms onset to MR scan was 12.8 ± 6.4 hours. All patients with any type of MES had new lesions on their DWI MR scan. No statistically significant difference existed between benign and malignant MES groups regarding DWI lesion number (5.6 ± 2.1 vs 7.6 ± 4.5; P=0.482). The baseline DWI lesion volume was significantly larger in the malignant MES group (21.6 ± 23.8 mL) than in the benign MES group (3.89 ± 6.70 mL; P=0.008; Table 2).

Out of 92 patients, 65 patients (70.7%) underwent MR scan with DWI within 48 hours from symptoms onset. All MES-positive patients underwent MRI. Twenty-seven patients (27/92; 29.3%) were not eligible for MR scan because of metals in the body, claustrophobia, obesity, or cardiac pacemaker. The mean time from symptoms onset to MR scan was 12.8 ± 6.4 hours. All patients with any type of MES had new lesions on their DWI MR scan. No statistically significant difference existed between benign and malignant MES groups regarding DWI lesion number (5.6 ± 2.1 vs 7.6 ± 4.5; P=0.482). The baseline DWI lesion volume was significantly larger in the malignant MES group (21.6 ± 23.8 mL) than in the benign MES group (3.89 ± 6.70 mL; P=0.008; Table 2).

Sixty-four patients (69.6%, 64/92) underwent CT angiogram of the neck vessels within 12 hours of symptoms onset (malignant MES group, 7/9 [77.8%]; benign MES group, 11/17 [64.7%]). Twenty-eight patients (28/92; 30.4%) were not eligible for CT angiogram because of renal insufficiency, allergy to dye, and other reasons. Malignant MES group had

**Table 1. Comparisons of Parameters Between Benign MES Group and Malignant MES Group**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Benign MES (Mean ± SD)</th>
<th>Malignant MES (Mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counts</td>
<td>263 (82.4%)</td>
<td>56 (17.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>REIM (joule×10⁻¹⁶)</td>
<td>0.4±0.2</td>
<td>2.1±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MaxI, dB</td>
<td>8.5±3.2</td>
<td>19.3±5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MaxD, msec</td>
<td>52.9±12.7</td>
<td>104.8±260.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MGTT, msec</td>
<td>76.4±36.4</td>
<td>168.3±640.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DIST, mm</td>
<td>17.8±9.1</td>
<td>37.5±8.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VM, cm/sec</td>
<td>25.2±16.4</td>
<td>24.6±9.4</td>
<td>0.73</td>
</tr>
<tr>
<td>Diameter, μm</td>
<td>275.2±98.2</td>
<td>1009.1±466.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Arterial trajectory**

<table>
<thead>
<tr>
<th></th>
<th>Benign MES (Mean ± SD)</th>
<th>Malignant MES (Mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1-M2</td>
<td>48 (18.3%)</td>
<td>51 (91.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACA</td>
<td>11 (4.2%)</td>
<td>1 (1.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M1</td>
<td>128 (48.7)</td>
<td>3 (5.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M2</td>
<td>14 (5.3%)</td>
<td>1 (1.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perforator</td>
<td>41 (15.6%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICA</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M1 distal</td>
<td>20 (7.6%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACA indicates anterior carotid artery; DIST, travel distance of microembolus; ICA, internal carotid artery; MaxD, maximum duration of microembolus in a 3-mm gate; VM, velocity of microembolus.

**Figure 3.** An example of malignant MES and benign MES A typical malignant MES (arrow) and benign MES (arrow head) are seen in the PMD display. In this example, the malignant MES is well-differentiated from benign MES (REIM, 3.0 vs 0; MaxI, 20 dB vs 3 dB; MaxD, 150 ms vs 50 ms; MGTT, 220 ms vs 80 ms; DIST, 35 mm vs 20 mm; velocity of MES, 15.9 cm/sec vs 20 cm/sec).
Table 2. Comparison of Baseline Characteristics, DWI Lesion Volume, Patterns of CTA, and Recurrent Stroke/TIA of Benign MES and Malignant MES Groups

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Benign MES Group</th>
<th>Malignant MES Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke (%)</td>
<td>13 (76.5)</td>
<td>8 (88.9)</td>
<td>0.452</td>
</tr>
<tr>
<td>Total MES count</td>
<td>5.3±8.3</td>
<td>25.1±22.1</td>
<td>0.002</td>
</tr>
<tr>
<td>N of patients (%)</td>
<td>17 (65.4)</td>
<td>9 (34.6)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (70.6)</td>
<td>3 (33.3)</td>
<td>0.079</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3 (17.6)</td>
<td>1 (11.1)</td>
<td>0.569</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (29.4)</td>
<td>3 (33.3)</td>
<td>0.587</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>4 (23.5)</td>
<td>3 (33.3)</td>
<td>0.462</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>2 (11.8)</td>
<td>9 (0.0)</td>
<td>0.418</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>4 (23.5)</td>
<td>2 (22.2)</td>
<td>0.668</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (29.4)</td>
<td>3 (33.3)</td>
<td>0.587</td>
</tr>
</tbody>
</table>

Medications before index stroke/TIA

| Antiplatelet agents | 9 (52.9) | 5 (55.6) | 0.613 |
| Statin              | 10 (58.8) | 4 (44.4) | 0.387 |
| NIHSS baseline, median (IQR) | 2 (0–2) | 4 (1.5–12) | 0.218 |
| NIHSS at 90 days, median (IQR) | 1 (0–2) | 4 (0–8) | 0.025 |
| Modified Rankin Scale score at 90 days, median (IQR) | 0 (0–1) | 3 (0–4) | 0.025 |

MRI

| DWI lesion N       | 5.6±2.1       | 7.6±4.5       | 0.482 |
| DWI lesion volume, mL | 3.89±6.70     | 21.6±23.8     | 0.008 |

CTA for carotid artery

<table>
<thead>
<tr>
<th>Interventions for secondary prevention</th>
<th>Benign MES Group</th>
<th>Malignant MES Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation</td>
<td>4 (23.5)</td>
<td>8 (88.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Carotid endarterectomy/stent</td>
<td>3 (17.6)</td>
<td>7 (77.8)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Discussion

Our study has demonstrated the capability of PMD TCD to define the emboli signals based on quality of MES. This has resulted in the identification of a subgroup of emboli defined as malignant MES. These emboli have characteristics exhibiting a higher energy level signature, which represent a greater mass than the typical MES based on quantum physics principles. We found that this subgroup of MES is associated with larger size of baseline infarct and more frequent intraluminal thrombus of carotid artery. In addition, patients with malignant MES on TCD monitoring are more prone to poor clinical outcome and receiving more aggressive treatment for prevention of recurrent stroke. Defining this subgroup of patients with acute TIA/stroke and malignant MES could help the physician in preventing further stroke recurrence by optimizing medical treatment or in justifying early revascularization.

Our findings may be of significant clinical importance because the focus of prevention treatment using MES as a surrogate outcome has solely rested on the frequency or presence of MES. All therapeutic studies to date have measured treatment effect by the reduction in MES counts with a variety of therapies.24–27 The number of MES likely has some importance in predicting risk of stroke, as best demonstrated by Levi et al28 in the dextran study of carotid endarterectomy candidates, which reported a 77% chance of stroke if >50 MES occurred per hour. Subsequent work suggested detection rate >10 MES per 30 minutes was associated with high postoperative stroke rate.29 The importance of the commonly seen MES counts of (1–10 MES per hour) is much less clear. At these levels, MES appears to have only modest predictive value for subsequent clinical stroke events and, therefore, only limited value in stroke prevention. The detection of subgroup of malignant MES may define a more malignant course that may require aggressive antithrombotic treatment and more urgent revascularization.

PMD has significant advantages over single-gate spectrogram TCD by providing the necessary information to evaluate the “size” of MES. The size of embolus could influence the back-scatter cross-section,30 which would be estimated indirectly by measured embolus-to-blood ratio.31 Measured embolus-to-blood ratio can be converted into MaxI on PMD display, which represents maximal power of MES.18 Power-based methods using measured embolus-to-blood ratio (MaxI on PMD display) are most promising28; however, sound intensity for solid emboli (for example, red cell aggregate) does not increase monotonically with power; therefore, any 1 value of MaxI on PMD display could correspond to 2 or 3 different embolus sizes.13 For this reason, the MaxI is not considered sufficient to characterize size of emboli unless other information is simultaneously provided. Distance of travel of MES may have some advantages over the MaxI on PMD display because it is not affected by amplifier overload.13 However, it can be influenced by insonation status, such as bone window or the sonographer’s skill. MES duration measurement is another promising approach,14
which could be longer in the case of larger emboli. However, the duration of MES can also be affected by velocity of MES and hemodynamic status of patients. If the size of MES is considered to be proportionate in its mass because the density of embolus, such as red cell aggregates, is homogenous, then relative energy level of MES can be calculated by product of power as measured sound intensity (MaxI on PMD display) and duration of MES (maximum duration on PMD display).

Even though presence of malignant MES failed to demonstrate more frequent subsequent vascular event such as stroke/TIA in our study, the tendency toward higher risk of recurrent stroke/TIA in the malignant MES group was distinct (3/9 [33.3%] vs 2/17 [11.8%]). Also, it needs to be considered that finding malignant MES on TCD monitoring led the physicians to commence more aggressive treatment, such as early anticoagulation or carotid endarterectomy/stent for secondary stroke prevention. There was a lack of power attributable to low number of patients in our study. Validation of this sizing method is required with a controlled study using various sizes of imaging contrast nanobubbles. In addition, large-scale clinical trials using malignant MES as a surrogate outcome could also confirm the relationship between malignant MES and prognosis.

Our study suggested that most of the emboli produced by carotid stenosis were smaller than the mean size of the penetrating artery. The more severe the carotid disease is, the more likely the MES is malignant. Judging from the analysis of arterial trajectory of embolus, malignant MES would preferentially enter the larger-circumferential cerebral arteries and smaller benign MES could enter any arteries, including the small perforating arteries that arise from the major vessels of the circle of Willis. MacDonald et al. reported that larger emboli had a significant tendency to enter larger arteries and smaller emboli were more likely to be distributed in the small perforating arteries. Embolism as a cause of lacunar infarction had been reported in 18% to 25% of cases.

Our study was limited in that we could not completely rule out air bubbles as the cause of the high-intensity MES seen in the malignant MES group. However, this would seem very unlikely because patients who had undergone mechanical valvular disease or any type of surgery with air entry into the vasculature were excluded from the study. Another limitation is the fact that MaxI on PMD display is influenced by many factors, such as the size of MCA, shape of the ultrasonic beam, the emboli trajectory, and the interaction of these parameters. Another limitation of our study is that clinical outcome may not reflect the natural history of MES because positive MES at the time of admission were considered clinically significant, which caused the physician to initiate aggressive antithrombotic therapies. In addition, patients also underwent fairly urgent carotid endarterectomy or stenting if stenosis was appropriate (>50% stenosis), and this affects the long-term outcome. Therefore, this limitation should not overestimate the poor outcome seen in the malignant MES group; however, if it had an effect, it could underestimate that.

Conclusion
In conclusion, our results suggest that among patients with symptomatic carotid disease, there is a subgroup of patients with embolic signals defined as malignant MES that can be detected by PMD display. These malignant MES have the characteristics typical of a longer trajectory through the MCA vasculature, larger baseline infarcts, and worse clinical outcome. These malignant MES cases should be cause for concern and may require more aggressive antithrombotic treatment and investigation for intraluminal thrombus or plaque ulceration.

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None.

References

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Relative Energy Index of Microembolic Signal Can Predict Malignant Microemboli
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